AN INVESTIGATION OF THE EFFECTS PRODUCED UPON THE EXCRETION OF URINARY PIGMENTS BY SALTS OF QUININE

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In view of the preponderating rôle attributed to salts of quinine in the production of blackwater fever, it has been evident to me for some time that useful infoımation might be secured by examining the action exerted by these salts upon the blood of a healthy adult, living in a malarial country, who had become accustomed to their prophylactic use. It was possible that the action which these salts exerted upon the healthy differed only in the amount of the reaction from that which they exert in a case of disease. In the healthy, the action exerted would be more easily observed in the absence of the various complications introduced into such an investigation by an attack of malarial fever.

Then, the fact that the effect produced upon the urinary pigments by a prophylactic dose of quinine might be used as an index to that exerted on the blood suggested itself, and an examination of the effect of a single dose of the drug was undertaken.

The subject of the experiment was a healthy European adult, long resident in West Africa, where, on several occasions in previous years, he had suffered from attacks of malarial fever (malignant tertian).

The investigation was conducted as follows:—All urine passed between 9.30 p.m. (bedtime) and 7.30 a.m. (breakfast) was collected in a clean beaker for examination. This period of ten hours was selected because of its convenience, and because during this period the environmental conditions would remain fairly uniform; for no food or fluids would be taken, the temperature in bed would be nearly uniform, and the amount of sweating would be less subject to alteration by changes in temperature, amount of exercise, amount of clothing, or from leaving the shade of the house for the higher temperature out of doors.

An attempt was also made to keep the dietary as uniform as possible during the period of experiment. No fluids were taken except at meals, and then in equal measured amounts. The bowels were naturally opened twice a day, but there was no diarrhoea. The occupation was sedentary, a short walk being taken daily at sundown.

On the first day of the experiment all urine passed between 9.30 p.m. and 7.30 a.m. was collected to serve as a control, representing the normal excretion uninfluenced by the action of a salt of quinine. On the following night, at 9.30 p.m., a dose of fifteen grains of quinine hydrochloride (B. W. & Co.'s tabloids) was taken with six ounces of water, a similar amount of water having been taken on the first night and on all the subsequent nights of the experiment. All urine passed in the ten hours from 9.30 p.m. to 7.30 a.m. on the seven subsequent days was collected and a preliminary examination of the amount, colour, specific gravity, and reaction, was made.

It was then prepared for the photographing of its absorption spectrum in the following manner. The urine collected each morning was poured into a tall measuring cylinder, covered and placed before a well-lighted window for two hours, so as to ensure the complete conversion of urobilinogen to urobilin. Then 100 c.c. of this urine was placed in a beaker and rendered alkaline by the addition of a measured amount of ammonium hydrate (NH_4OH). The precipitated phosphates were removed by filtration, and to the clear filtrate a solution of zinc chloride ($ZnCl_2$) was added cautiously until the precipitate formed began to remain undissolved. The urine was then again filtered, poured into a Baly tube and at once photographed in a Hilger quartz spectrograph by acetylene gas light projected through a quartz condenser. By the use of a Baly tube it was possible to produce readily on the same plate a series of ten photographs taken through regularly diminishing depths of urine under such uniform conditions that the amount of absorption shown by the different depths could be compared; and on different days, when dealing with urine of varying specific gravity, a urine of low specific gravity could be compared with one of high specific gravity without the necessity of diluting the latter with water, a device likely to introduce a variable error.

The photographs were taken upon the Wratton and Wainwright's pan-chromatic plate. This plate, though the best procurable, is, unfortunately, very unequally sensitive to the different colours. The ratios given by the makers are: red, $\frac{1}{16}$; green, $\frac{1}{16}$; blue, $\frac{7}{8}$. And this fact must be borne in mind when interpreting the absence of any record in the blue region. This is not the only defect, however, for these plates also show three dark bands: one between C and D, one between D and E, and one between b and F, the plate being evidently relatively blind in these three places. These three bands are also present in photographs of the solar spectrum, and are therefore not due to the use of acetylene as an illuminant. This, of course, adds greatly to the difficulty of interpreting the absorption bands in these three regions, but has no appreciable effect on the steepness of the curve on each plate shown by each complete series of ten photographs.

The photograph of each day's urine will be seen to consist of twelve records in series. The first eleven of the series were photographed through a regularly diminishing depth of urine from 10 cm. to 0 cm. by steps of 1 cm. Number 11 in each series represents, therefore, the effect produced upon the plate when no urine was interposed, the other conditions remaining constant. In it, in one set of photographs, is shown the D, or sodium line, for purposes of orientation. In the first series of photographs this line is shown in the 12th record. In the second series of photographs the 12th record represents in all the spectrum of burning magnesium ribbon, and is intended to enable the solar line b to be located.

The exposures given to all the records on all the plates were accurately timed with a stop-clock and were equal. The plates were developed with the same developer for equal periods of time. The only variant was the temperature of the dark room, which varied about two degrees Fahrenheit. Thus, the factors likely to cause variation in the results, were kept as small as possible so as to make the records comparable with each other. There is one other variant, the daily average air temperature and range. I am unable to furnish these data as I am writing this in England, where I have no access to meteorological records. The mean temperatures of the two months, August and September, are, however, very much alike.

Two similar experiments were made upon the same subject: the first from 31st July, 1910, to 7th August, 1910, inclusive, and the second from 10th September, 1910, to 17th September, 1910, inclusive. During both periods, the subject's temperature remained normal, and parasites could not be found in his peripheral blood. Tables showing the results obtained, quantity, colour, reaction, etc., will be found below. In each table the first item represents the control, that is the urine collected before any quinine was administered. I have treated it as unity, or $\frac{10}{10}$, and it is with it that the results obtained for the seven subsequent days must be compared. The ratios thus obtained should then be compared with the photographic ratios.

Now, in estimating the results shown in these tables, the following facts are important:—

1. The amount of absorption required to extinguish the chemical or photographic effect on the pan-chromatic plate in the blue region, is, when compared with that required in the red or green, in the ratio of $\frac{7}{8}$: $\frac{1}{16}$. A control photograph is, therefore, absolutely necessary.

2. Under normal conditions the percentage of solids excreted daily in the urine is nearly constant, but the quantity of urine passed depending, as it does, on the water constituent, varies greatly.

The amount of solids and pigments in urine is therefore usually in the inverse ratio to the amount of water. It follows, therefore, that if there were in these samples no abnormal increase in the pigments, the ratio borne by the quantity of urine passed each ten hours to the control quantity would be similar to the ratio borne by the photographic records of each day to the photographic control.

For example:—Taking the photographic record of the 10th September, 1910, as control or unity, and comparing the steepness of the photographs of the seven subsequent days with it, a series of ratios can very readily be prepared. Then, taking the quantity of urine passed on 10th September, 1910, as the control or unity, and comparing the quantities passed on the seven subsequent days with it, another series of ratios can be calculated. Both these series of ratios are shown in the following tables:—

Data Obtained in Experiment I

31—7—10 to 7—8—10

Date	Quantity	Colour	Reaction
31—7—10	640 c.c.	Yellow	Acid
1—8—10	766 c.c.	Pale-yellow	,,
2—8—10	360 c.c.	Pale brown	,,
3—8—10	595 c.c.	Yellow	,,
4—8—10	605 c.c.	,, ...	,,
5—8—10	660 c.c.	,, ...	,,
6—8—10	690 c.c.	,, ...	,,
7—8—10	655 c.c.	,, ...	,,

Ratios

Date	Quantity Ratios	Absorption Ratios	A—Q
31—7—10	$\frac{10}{10}$	$\frac{10}{10}$	0·0
1—8—10	$\frac{12}{10}$	$\frac{10}{10}$	− 0·20
2—8—10	$\frac{5·6}{10}$	$\frac{16}{10}$	+ 1·00
3—8—10	$\frac{9}{10}$	$\frac{14}{10}$	+ 0·50
4—8—10	$\frac{9·4}{10}$	$\frac{14}{10}$	+ 0·46
5—8—10	$\frac{10·3}{10}$	$\frac{15}{10}$	+ 0·47
6—8—10	$\frac{10·7}{10}$	$\frac{11}{10}$	+ 0·03
7—8—10	$\frac{10·2}{10}$	$\frac{10}{10}$	− 0·02

Data Obtained in Experiment II

10—9—10 to 17—9—10

Date	Quantity	Colour	Reaction	Sp. gr.	Temperature	Sp. gr. reduced to 60° F.	Solids in 10 hours
							grms.
10—9—10	595 c.c.	Yellow ...	Acid	1013	84° F.	1021	29
11—9—10	803 c.c.	Pale yellow	,,	1010	80° F.	1018	33·6
12—9—10	235 c.c.	Pale brown	,,	1027	84° F.	1035	19·1
13—9—10	550 c.c.	Amber ...	,,	1021	84° F.	1029	23·6
14—9—10	530 c.c.	Pale amber	,,	1016	84° F.	1024	29·6
15—9—10	550 c.c.	Bright yellow	,,	1014	81° F.	1021	26·9
16—9—10	650 c.c.	Yellow ...	,,	1014	80° F.	1020·6	31·1
17—9—10	541 c.c.	,, ...	,,	1015	80° F.	1021·6	27·2

Ratios

Date	Quantity Ratios	Absorption Ratios	A—Q
10—9—10	$\frac{10}{10}$	$\frac{10}{10}$	0·0
11—9—10	$\frac{13}{10}$	$\frac{6}{10}$	− 0·70
12—9—10	$\frac{4}{10}$	$\frac{18}{10}$	+ 1·40
13—9—10	$\frac{9}{10}$	$\frac{14}{10}$	+ 0·50
14—9—10	$\frac{8·8}{10}$	$\frac{14}{10}$	+ 0·52
15—9—10	$\frac{9}{10}$	$\frac{15}{10}$	+ 0·60
16—9—10	$\frac{10·9}{10}$	$\frac{11}{10}$	+ 0·01
17—9—10	$\frac{9·1}{10}$	$\frac{11}{10}$	+ 0·19

The experience gained while carrying out the previous experiments enabled the last experiment to be performed with greater accuracy in detail, and the data of this experiment are, therefore, somewhat superior to those of the first experiment.

It will be seen, however, that the results obtained in both experiments agree fairly closely in essentials. I believe the following conclusions may be drawn from the results obtained in both :—

1. That a dose of fifteen grains of quinine hydrochloride causes an early increase in the amount of water excreted in the urine.

2. That this increase is followed within twenty-four hours by a marked decrease, which is accompanied by an increase in the excreted pigments.

3. That these pigments consist largely of urobilin (chemical and spectroscopic proofs).

4. That there is an approximate return to the normal elimination of water and pigment, the phase being almost completed in one week.

Subjective Sensations

The subjective sensations following a dose of quinine are best observed by a person who regularly takes one large weekly dose of the drug, for then the sequence of the sensations is observed to be very similar from week to week, and the regularity is sufficiently great to enable the operation of causes other than quinine to be excluded.

1. A dose of fifteen grains of quinine hydrochloride taken on Saturday night is followed, after an hour or so of restlessness, by sound sleep accompanied usually by pleasant dreams. Without quinine sleep is usually dreamless.

2. On the following day, Sunday, there is a feeling of some exhilaration, with deafness, ringing in the ears, some tremor of the hands, and an inclination for bodily and mental activity.

3. On Monday a certain amount of depression of spirits sets in, which lasts through Tuesday. Deafness continues almost unchanged, and sleep is not so sound.

4. The feeling of depression passes away by Wednesday night

or Thursday morning, when the aural effects have considerably subsided.

The increasing use of salts of quinine in malarial prophylaxis has added a continually increasing importance to the estimation of the effects produced by them upon persons who take a daily or weekly dose for long periods of time. The difficulties of the subject are, however, great, for even the condition of the quinine molecule while circulating with the blood is unknown, and there are no convincing proofs of the mechanism by which these salts exert their well-known destructive action on the malarial parasite.

Even the dosage is still a matter for debate, and there are no observations yet available showing the effects exerted by prophylactic doses of quinine upon the health, special senses, or excretions of a healthy person. At present it can only be affirmed that a European living in a malarious country such as West Africa has a choice of two alternatives:—

1. Recurring attacks of malaria.
2. Quinine prophylaxis.

Both alternatives are harmful, and it therefore becomes simply a question of which is least so.

Few experienced persons in West Africa would have any hesitation about deciding for quinine prophylaxis, and there are fewer still who would not wish that some other alternative were available permitting them to choose otherwise, for this long continued daily or weekly use of quinine produces at least in a certain percentage of Europeans some of the following evil effects:—

1. Diminished acuity of hearing.
2. Premature onset of presbyopia.
3. Mental depression.
4. Dyspepsia and skin affections.

So long then as the proximity of an infected native population and of suitable anophelines makes such prophylaxis necessary for European existence, so long the following questions will possess both a practical and theoretical interest:—

I. At what rate is a salt of quinine excreted?

II. Is the amount of excretion in direct or inverse ratio to the amount of the dose?

III. How long does it exert an influence upon the subjective sensations of the person?

IV. What changes does a full dose of a salt of quinine exert upon the urinary pigments, salts, acidity, specific gravity, etc., and does this effect differ in healthy persons and in persons harbouring the malarial parasite?

No. I. The practical importance of this question will be appreciated when the following points are considered:—

1. The whole of a dose of a salt of quinine cannot be recovered from the excretion during the first twenty-four hours after administration.

2. Many persons are taking daily throughout the year a dose of five grains of quinine.

3. A cumulative action of the drug would seem to be a necessary contingency from these premises.

4. Does the drug accumulate in the body, and, if so, how is its cumulative action manifested?

No. II. An answer to this question would enable the safest and most efficient dose to be fixed.

No. III. Answers to this question would enable an estimate to be made of the influence exerted by idiosyncracy, and of its relation to the effect produced upon the special senses.

No. IV. Of all these, the question of the effect exerted upon the elimination of the urinary pigments appears to be most important, especially the effect exerted upon those pigments derived directly from haemoglobin; for an increased excretion in the urine of such pigments would be likely to follow any increased destruction of red blood corpuscles This applies with special force to the urobilin, the excretion of which, in both urine and faeces, is known to be increased in diseases favouring abnormal destruction of red blood corpuscles. A personal or partial answer to part of question No. IV is furnished by these experiments, but further observation made upon other persons are required to enable the amount of the personal factor or idiosyncracy to be estimated. To exclude the possible influence on the results of malarial infection, similar experiments in a non-malarious country upon persons who have never suffered from malaria are very desirable. It is for this reason that I have explained in the present article so very fully the methods by which my results have been obtained.

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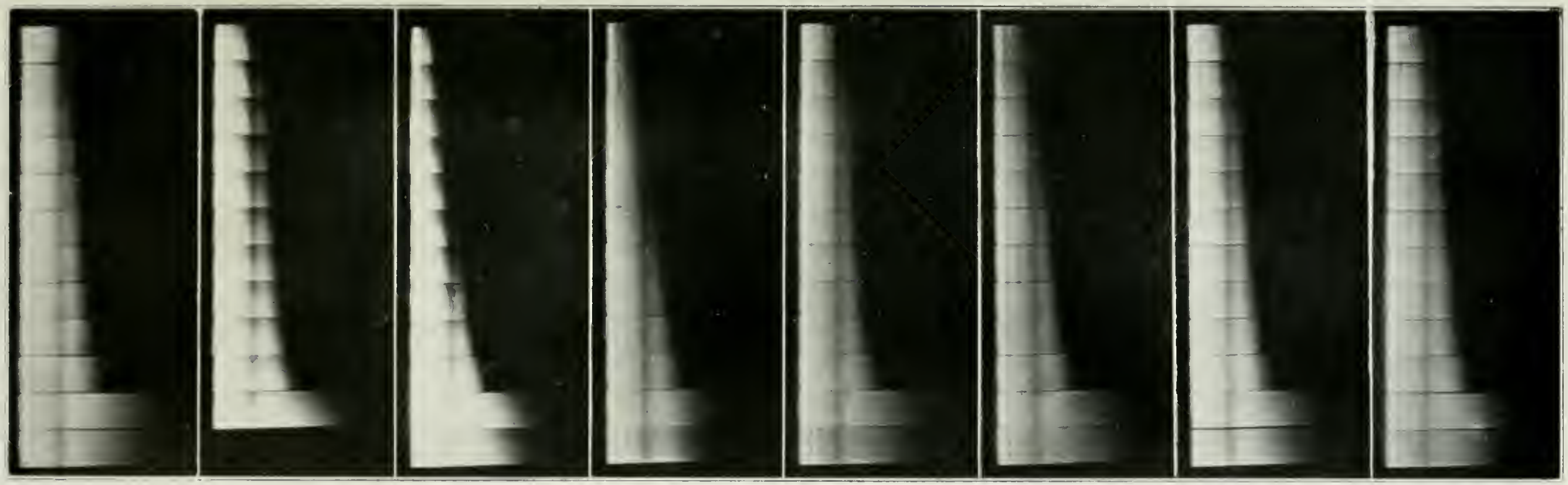

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